Amendments to the Specification

Please replace the paragraph beginning at p. 2 line 10 with the following replacement paragraph:

Other 2,3-benzodiazepines that are structurally similar to tofisopam have been investigated and shown to have varying activity profiles. For example, GYKI-52466 and GYKI-53655 (structures shown below) act as non-competitive glutamate antagonists at the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) site, and have demonstrated neuroprotective, muscle relaxant and anticonvulsant activity (*Id.*). Another group of 2,3-benzodiazepines that has been investigated are represented by the compound GYKI-52895, and show activity as selective dopamine uptake inhibitors with potential use in antidepressant and anti-Parkinsonism therapy.

Please replace the paragraph beginning at p. 3 line 23 with the following replacement paragraph:

The optically pure (*R*)-enantiomer of tofisopam (R)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine) has been isolated and shown to possess the non-sedative anxiolytic activity of the racemic mixture. See U.S. Patent 6,080,736; the entire disclosure of which is incorporated herein by reference.

Please replace the paragraph beginning at p. 5 line 14 with the following replacement paragraph:

The cause of fever may be infectious or non-infectious (e.g., inflammatory, neoplastic, and immunologically mediated disorders). The pattern may be intermittent, characterized by daily spikes followed by a return to normal temperature, or remittent, in which the temperature does not return to normal. The elderly often have a diminished fever response. Certain patients, *e.g.*, alcoholics, the very old, and the very young, may become hypothermic in response to severe infection. *Id.*

Please replace the paragraph beginning at p. 6 line 13 with the following replacement paragraph:

Drugs that inhibit cyclooxygenase are effective in reducing fever; those used most often are acetaminophen, aspirin, and other NSAID[[']]s. Although corticosteroids also reduce fever, they should not be used expressly for this purpose because of their other effects on the immune system.

Please replace the paragraph beginning at p. 6 line 19 with the following replacement paragraph:

Serotonin syndrome is caused by excess stimulation of post-synaptic 5-hydroxytryptamine receptors in the brain stem and spinal cord, typically the result of combining serotonergic agents with monoamine oxidase inhibitors (MAOI[[']]s). There is no effective drug treatment established.

Please replace the paragraph beginning at p. 7 line 1 with the following replacement paragraph:

Serotonin syndrome is generally caused by a combination of two or more drugs, one of which is often a selective serotonergic medication. The drugs which are known to frequently contribute to this condition are combinations of MAOI[[']]s with fluoxetine (Prozac) and other selective Serotonin Reuptake Inhibitors (SSRI[[']]s) or other drugs that have a powerful effect upon serotonin, *i.e.*, clomipramine (Anafranil), trazadone (Deseryl), *etc.* The combination of lithium with these selective serotonergic agents has been implicated in enhancing serotonin syndrome. The tricyclic antidepressants, lithium, MAOI[[']]s, SSRI[[']]s, electric shock treatment, tryptophan, and the serotonin agonists (fenfluramine) all enhance serotonin neurotransmission and can contribute to the syndrome. Any factors that raise the level of serotonin can bring on this hyperserotonergic condition.

Please replace the paragraph beginning at p. 7 line 13 with the following replacement paragraph:

The published reports since 1982 indicate that in human patients, if the serotonergic medication is discontinued, the syndrome will often resolve on its own within twenty-four hours. Supportive measures can be used, however to ameliorate serious symptoms such as hyperthermia. These include cooling blankets for hyperthermia, intramuscular chlorpromazine as an antipyretic and sedative agent, artificial ventilation for respiratory insufficiency, anticonvulsants for seizures, clonazepam for myoclonus, and nifedipine for hypertension. See, A. B. Tracy, "Prozac: Panacea Or Pandora?" Cassia Publications, 1993, p. 88; the entire disclosure of which is incorporated herein by reference.

Please replace the paragraph beginning at p. 8 line 9 with the following replacement paragraph:

The symptom of disturbance of normal thermoregulation, commonly referred to as "hot flashes" is a frequent clinical observation in postmenopausal women. The term "hot flash" refers to any sudden, brief, sensation of heat, often over the entire body, such as that experienced by many women during menopause. Hot flashes may also be drug induced by anti-estrogen compounds such as tamoxifen, toremifen and raloxifen, or by removal of estrogen-producing tissues, *e.g.*, abdominal hysterectomy, ovariectomy and bilateral salpingo-oopherectomy, or by organ failure of estrogen producing organs such as the ovaries. See, Loprinzi *et al.*, *Clin. Breast Cancer* 2000 April;1(1):52-6; the entire disclosure of which is incorporated herein by reference. Drug induced hot flashes are not limited to women, occurring often in men undergoing cancer therapy, e.g., for example, tamoxifen therapy for prostate cancer.

Please replace the paragraph beginning at p. 9 line 13 with the following replacement paragraph:

Numerous chemical entities have been investigated for biological activity in the symptomatic treatment of menopause. Particular classes of compounds which have been

investigated include estrogen agonists, progesterone agonists, drug formulations comprising both an estrogen agonist and a progesterone agonist, selective estrogen receptor modulators, bisphosphonates, selective serotonin reuptake inhibitors (SSRIs), norepinephrine serotonin reuptake inhibitors (NSRIs) and gamma aminobutyric ~~aminobuteric~~ acid (GABA) modulators.

Please replace Table 1, immediately following p. 9 line 22 with the following replacement table:

Table 1

Drug Class	Exemplary compounds
estrogen agonists	Estradiol
Formulations comprising an estrogen agonist and a progesterone agonist	estradiol/trimegestrone
progesterone agonists	trimegestrone
selective estrogen receptor modulators	raloxifene bazedoxifene
bisphosphonates	risedronic acid ibandronic acid
SSRIs	fluoxetine paroxetine
NSRI	venlafaxine
GABA modulator	gabapentin

Please replace the paragraph beginning at p. 11 line 1 with the following replacement paragraph:

What are [[is]] needed are new agents that effectively lower body temperature in instances wherein the body temperature is abnormally high and in instances wherein lowering the body temperature to a level below normal body temperature provides a therapeutic benefit.

Please replace the paragraph beginning at p. 18 line 10 with the following replacement paragraph:

Preferably, the at least one additional therapeutic agent is selected from the group consisting of estrogen agonists, progesterone agonists, selective estrogen receptor modulators, bisphosphonates, selective serotonin reuptake inhibitors (SSRIs), norepinephrine serotonin reuptake inhibitors (NSRIs) and gamma aminobutyric ~~aminobuteric~~ acid (GABA) modulators.

Please replace the paragraph beginning at p. 18 line 16 with the following replacement paragraph:

According to yet another embodiment of the invention, there is provided a composition comprising at least one compound of Formula I as defined herein, and at least one additional therapeutic agent, wherein the at least one additional therapeutic agent is selected from the group consisting of estrogen agonists, progesterone agonists, selective estrogen receptor modulators, bisphosphonates, selective serotonin reuptake inhibitors (SSRIs), norepinephrine serotonin reuptake inhibitors (NSRIs) and gamma aminobutyric ~~aminobuteric~~ acid (GABA) modulators.

Please replace the paragraph beginning at p. 18 line 25 with the following replacement paragraph:

The phrase "optically active" refers to a property whereby a material rotates the plane of plane-polarized light. A compound that is optically active is non-superimposable on its mirror image. The property of non-superimposablity of an object on its mirror image is called chirality.

Please replace the paragraph beginning at p. 18 line 29 with the following replacement paragraph:

The property of "chirality" in a molecule may arise from any structural feature that makes the molecule non-superimposable on its mirror image. The most common structural feature producing chirality is an asymmetric carbon atom, i.e., a carbon atom having four nonequivalent groups attached thereto.

Please replace the paragraph beginning at p. 19 line 1 with the following replacement paragraph:

The term "enantiomer" refers to each of the two non-superimposable isomers of a pure compound that is optically active. Single enantiomers are designated according to the *Cahn-Ingold-Prelog* system, a set of priority rules that rank the four groups attached to an asymmetric carbon. See March, Advanced Organic Chemistry, 4th Ed., (1992), p. 109. Once the priority ranking of the four groups is determined, the molecule is oriented so that the lowest ranking group is pointed away from the viewer. Then, if the descending rank order of the other groups proceeds clockwise, the molecule is designated *R* and if the descending rank of the other groups proceeds counterclockwise, the molecule is designated *S*. In the example below, the *Cahn-Ingold-Prelog* ranking sequence id A>B>C>D. The lowest ranking atom, D is oriented away from the viewer.

Please replace the paragraph beginning at p. 20 line 12 with the following replacement paragraph:

The term "effective amount" when used to describe therapy to lower the body temperature of an individual suffering from hot flashes, particularly hot flashes associated with menopause, refers to the amount of a compound of Formula I, or of a combination of a compound of Formula I with one or more additional agents, e.g., estrogen agonists, progesterone agonists, selective estrogen receptor modulators, bisphosphonates, SSRIs, NSRIs and gamma aminobutyric acid (GABA) modulators.

Please replace the paragraph beginning at p. 22 line 1 with the following replacement paragraph:

Examples of polycyclic heterocycles include: [[I]]indole, indoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, cinnoline, quinoxaline, quinazoline, 1,4-benzodioxolane, 1,4-benzodioxepane, 1,3-benzodioxane, ~~and~~ coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, 1,2-benzisoxazoline, benzothiophene, benzoxazoline, benzthiazoline, purine, benzimidazoline, particularly 2-benzimidazoline, benztriazoline, thioxanthine, carbazole, carboline, acridine, pyrrolizidine, and quinolizidine.

Please replace the paragraph beginning at p. 24 line 12 with the following replacement paragraph:

Hot flashes treatable by the method of the invention include, for example, hot flashes associated with variation in hormone levels, *e.g.*, those occurring during menopause or perimenopause; hot flashes which occur as a side-effect of a drug therapy, for example an anti-estrogen therapy comprising administration of tamoxifen, toremifen or raloxifen, for example; hot flashes that occur subsequent to the removal of estrogen-producing tissues, e.g., abdominal hysterectomy, ovariectomy and bilateral salpingo-oopherectomy; and hot flashes that occur subsequent to organ failure of organs, such as the ovaries, which produce estrogen.

Please replace the paragraph beginning at p. 30 line 8 with the following replacement paragraph:

Chiral α_1-acid glycoprotein is a highly stable protein immobilized onto spherical silica particles that tolerates high concentrations of organic solvents, high and low pH, and high temperatures. Human serum albumin, though especially suited for the resolution of weak and strong acids, zwitterionic and non-protolytic compounds, has been used to resolve basic compounds. CBH is a very stable enzyme that has been immobilized onto spherical

silica particles and is preferentially used for the separation of enantiomers of basic drugs from many compound classes.

Please replace the paragraph beginning at p. 31 line 16 with the following replacement paragraph:

Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, ~~salicyclic, salicyclic,~~ 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, ~~algenic,~~ beta-hydroxybutyric, salicylic, ~~salicyclic,~~ galactaric and galacturonic acid.

Please replace the paragraph beginning at p. 32 line 24 with the following replacement paragraph:

For treating or preventing disorders associated with elevated body temperature or disorders wherein lowering the body temperature below the normal body temperature has therapeutic benefit, the specific dose of compound according to the invention to obtain therapeutic benefit will, of course, be determined by the particular circumstances of the individual patient including, the size, weight, age and sex of the patient. Also determinative will be the nature and stage of the disease and the route of administration. For example, a daily dosage of from about 100 to 1500 mg[[/kg]]/day may be utilized. Preferably, a daily dosage of from about 100 to 1000 mg[[/kg]]/day may be utilized. More preferably, a daily dosage of from about 100 to 500 mg[[/kg]]/day may be utilized. Higher or lower doses are also contemplated.

Please replace the paragraph beginning at p. 33 line 20 with the following replacement paragraph:

In addition, one or more compounds of Formula I may be administered to lower the body temperature of an individual suffering from hot flashes, particularly hot flashes associated with menopause, in combination with one or more additional therapeutic agents. Such additional agents include estrogen agonists, progesterone agonists, selective estrogen receptor modulators, bisphosphonates, SSRIs, NSRIs and gamma aminobutyric acid (GABA) modulators.

Please replace the paragraph beginning at p. 34 line 4 with the following replacement paragraph:

Bisphosphonates believed useful in combination with compounds of Formula I in methods of the invention include, for example, risedronic acid and ibandronic acid.

Please replace the paragraph beginning at p. 35 line 13 with the following replacement paragraph:

For parenteral administration, the active agent may be mixed with a suitable carrier or diluent such as water, an oil (particularly a vegetable oil), ethanol, saline solution, aqueous dextrose (glucose) and related sugar solutions, glycerol, or a glycol such as propylene glycol or polyethylene glycol. Solutions for parenteral administration preferably contain a water-soluble salt of the active agent. Stabilizing agents, antioxidizing agents and preservatives may also be added. Suitable antioxidizing agents include sulfite, ascorbic acid, citric acid and its salts, and sodium EDTA. Suitable preservatives include benzalkonium chloride, methyl- or propyl-paraben, and chlorbutanol. The composition for parenteral administration may take the form of an aqueous or non-aqueous solution, dispersion, suspension or emulsion.

Please replace the paragraph beginning at p. 35 line 13 with the following replacement paragraph:

The test animals were isolated in an experimental room approximately one hour before lights off on the day before the test. On the day of testing, animals were taken quietly from the cage, held in a supine position, the rectal temperature was measured and the animal was placed back into the cage. The same procedure was repeated 10 minutes later. The first temperature (T_1), the second temperature (T_2) and the difference (delta T) were recorded. The test compounds were administered <u>intraperitoneally</u> ~~intraperitonealy~~ 60 minutes before T_1, in order to prevent the stress of being injected from affecting the temperature measurements.